The Rejections under 35 USC 112, second paragraph

Claims 1-7, 11-12, 14-15, 17-182, 0 and 22-27 have been rejected under 35 USC 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as their invention. Applicants traverse certain aspects of this rejection and have amended in response to other aspects of this rejection.

The term "plurality" in claims 1, 2, 11, 20 and 23 is alleged to be a relative term which renders the claims indefinite. New claims 31, 41, 42, 50, 52 and 53 specify "at least two layers of carbon" or "layers" instead of a plurality of layers of carbon.

The term "capable of" is allegedly vague and indefinite. This language is not recited in new claims 31, 32 and 50, which replace as-filed claims 1, 2 and 20, and the step of binding at least some of said particles to said fibrin is now recited.

The term "portion" allegedly renders the claim indefinite. In new claims 31, 32 and 41, which replace as-filed claims 1, 2 and 11, the language "some of" is used. Applicants maintain the previous recitation was clear, but approval of the current language is requested.

The term "source" in claim 2 is allegedly vague and indefinite. New claim 32, which replaces claim 2, recites "a fibrin-containing source", which is believed abundantly clear.

The term "aqueous medium or solution" is allegedly vague and indefinite, as it is allegedly not clear what difference exists between an aqueous medium and an aqueous solution. The specification is said not to further define this phrase. In the interest of advancing prosecution and without acquiescing to this rejection, the new claims recite "aqueous solution".

The phrase "100 ng or less" is allegedly vague and indefinite and confusing in claims 7 and 27. In the interest of advancing prosecution and without acquiescing to this rejection, new claims 37

and 57 recite "up to 100 ng". Applicants respectfully submit that one of ordinary skill in the rat would not interpret the claims as encompassing a dosage of 0.

Claim 7 is alleged to be indefinite for ending with two periods. Applicants have corrected the double period in new claim 37.

The phrase "discrete particles" is allegedly indefinite, as it is allegedly unclear as to the distinction between particles and discrete particles. Applicants respectfully submit that this language is perfectly clear to one of ordinary skill in the art. Applicants maintain on the record that this term is understood to mean particles which are not aggregated, but rather, are separate, individual particles.

The phrase "selectively bind" is allegedly a relative term which renders claim 11 indefinite. Applicants respectfully maintain that the meaning of the recitation of "preferentially bind to fibrin over other blood plasma proteins" is perfectly clear and will be readily understood by one ordinary skill in the art.

The phrase "particles selectively bind to fibrin with a binding efficiency greater than the binding efficiency of said particles with other blood plasma proteins" is allegedly indefinite and confusing. Applicants respectfully maintain that the meaning of the recitation of "selectively bind to fibrin with a binding efficiency greater than the binding efficiency of said particles with other blood plasma proteins" is perfectly clear and will be readily understood by one ordinary skill in the art to mean binding with higher affinity to fibrin than to other blood plasma proteins.

The phrase "at least an outer layer of said layers being chemically modified to permit a stable chemical association of the layer with aqueous medium or solution" is allegedly indefinite. Applicants respectfully maintain that the language referred to by the Examiner is perfectly clear and requires no amendment. Chemical association includes hydrogen bonding and ionic binding and is well known and distinguished from physical association (i.e. by van der Waals interactions).

Stable as used in the claim is intended to mean "non-reactive" as would be readily understood by one of ordinary skill in the art. The term "permit" has been replaced, although it is maintained that the original language was abundantly clear to one of ordinary skill in the art.

The phrase "radiometric" is allegedly vague and indefinite as it is allegedly unclear as to the detection technique. Applicants respectfully maintain that this term is correct and is in no way vague or indefinite. Radiometric is a term used in the art and understood in the art.

The semicolon in claim 18, line 2, is allegedly indefinite as it is allegedly unclear if Gd and Au are part of the Markush group. New claim 48, which replaces claim 18, does not include a semicolon or a Markush group.

The term "some" in claim 20, line 6, is allegedly a relative term which renders the claim indefinite. Applicants respectfully submit that this term is perfectly clear, and they request that the Examiner suggest alternative language to convey the meaning that not all of the particles have the particular characteristic recited in new claim 50, which replaces claim 20.

The phrase "fibrin site" is claim 20, line 8, is allegedly vague and indefinite. New claim 50, which replaces claim 20, clarifies that the fibrin site is a localized fibrin site.

In view of the language of the amended claims and the clarifications provided above, Applicants respectfully maintain that the claims meet the requirements of 35 USC 112, second paragraph, and the withdrawal of the rejection is respectfully requested.

<u>The Rejections under 35 USC 103</u>

Claims 1-23 have been rejected as allegedly unpatentable over Burch et al. (Nuc. Med. Commun.) in view of Chignier et al. (Biomat.) in further view of Watson et al. (WO 93/15768) and Senden et al (J. Nuc. Med.). Applicants respectfully traverse this rejection.

The cited Burch reference is said to teach technegas as a new ventilation agent for lung scanning, wherein technegas is an ultrafine dispersion of technetium-labeled carbon. The particles are said to be less than 5 nm and the technegas is said to adhere to the walls of the alveoli. The Patent Office has acknowledged that the reference does not teach fibrin and therapeutic drugs.

Chignier is said to teach haemocompatibility and the biological course of carbonaceous composites for cardiovascular devices. This reference is said to disclose that in the presence of blood, fibrin meshes form over carbon-coated implants.

The Watson reference is said to teach the use of non-diamond carbon allotropes in diagnostic and therapeutic agents. ^{99}Te is disclosed as a radionuclide complexed with non-diamond carbon allotropes, and its use in *in vivo* and *in vitro* methods of imaging and treatment are taught. Aqueous media and solutions are taught as carriers.

The Senden reference is alleged to teach the physical and chemical nature of technegas as a radio tracer in lung ventilation scintigraphy. This reference indicates that technegas contains discrete radiolabeled fullerenes.

The Patent Office has concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Burch et al. using the teachings of the Chignier reference and obtain a detectable reagent for detecting fibrin because both Burch and Chignier teach carbonaceous compounds for use in the bloodstream and because Chignier teaches carbon-coated implants covered by a fibrin mesh. It has been further alleged that it would have been obvious to modify the invention of the combined references using the teachings of Watson et al. and Senden et al. and obtain a method of targeting a drug to a fibrin site because the combined references teach graphite carbons as diagnostic agents, Watson teaches combination with fullerenes, graphite carbons or amorphous carbons with diagnostic or therapeutic agents and Senden suggests that technegas contains discrete radiolabeled fullerenes.

The cited Burch reference teaches the use of technegas particles in aerosol form, immediately after they are generated, in the imaging of lung tissue. The particles are inhaled and then coat the surfaces of the lungs accessible to the inhaled air and particles. The Burch reference does not teach or suggest the use of the technegas in aqueous settings nor does it teach or suggest its use in circulation.

The cited Chignier reference teaches the biocompatibility of carbonaceous composites for cardiovascular devices. Carbon-silicon composites and carbon-carbon composites are taught. It appears that the carbon-containing material of this reference are glassy or fibrous, rather than small discrete particles. After the materials were implanted into a patient, there was at least partial coating with fibrin and/or cells. The present invention as claimed does not relate to implanted devices or other materials. This reference appears to teach (last paragraph) that the surfaces should be highly smooth and inert. This teaching is dramatically different from a method which requires discrete particles to be introduced into circulation. In addition, there is no teaching of how to label the carbon or how to disperse particles in solution.

The cited Senden reference relates to the use of aerosol technegas and methods for producing same. There is no teaching or suggestion of the dispersed nature of discrete particles in aqueous solution, as taught in the present application and required by the claims.

The cited Watson publication relates to the use of fullerenes and met-cars to carry diagnostic or therapeutic agents. This reference provides no teaching or suggestion of how to disperse the carbon species in solution. The dispersed nature of the particles (i.e,, the discrete particles) of the present invention is **crucial** to the usefulness of the particles in the fibrin imaging. The hydrophobic particles cannot be dispersed unless the surface is chemically modified or a steric polymer coating is bound to the surface.

Combining the cited references does not lead to the present invention. The key aspect missing from the cited references is the dispersed nature and discrete particles of the labeled

carbon. The present claimed methods are absolutely dependent on the dispersion of discrete particles in aqueous environments and the specific binding to fibrin. Not only do the cited references fail to teach or suggest the present invention, the cited references provide no teaching that enables the present invention. Accordingly, the present invention would not have been obvious to one of ordinary skill in the art and the invention as claimed is not *prima facie* obvious over the cited art, and the rejection must be withdrawn.

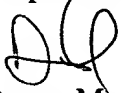
Conclusion

Based on the foregoing, this case is considered to be in condition for allowance and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time (one month) and a check in the amount of $110.00) as required by 37 CFR 1.17. If the amount submitted is incorrect, the undersigned authorizes that any deficiency in the enclosed fees be charged or any excess be credited to Deposit Account No. 07-1969. If the extension requested is insufficient, please consider as the necessary petition and charge the Deposit Account any additional fees.

Respectfully submitted,



Donna M. Ferber
Reg. No. 33,878

GREENLEE, WINNER AND SULLIVAN, P.C.
5370 Manhattan Circle, Suite 201
Boulder, CO 80303
Telephone (303) 499-8080
Facsimile: (303) 499-8089
Email: winner@greenwin.com
Attorney docket No.5-00
bmk: May 13, 2002